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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,668	03/19/2004	William A. Zoghbi	HO-P02680US1	8004

26271 7590 04/11/2007
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EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,668	ZOGHBI ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. The response filed 22 January 2007 is acknowledged. Response to Applicants arguments is found below.

Response to Arguments

Rejections Maintained

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. The rejection of claims 1, 2, 3, 4, 5, 6, 9, 10, 13, 18, 19, 20, 21 and 22 under 35 U.S.C. 102(b) as being anticipated by Nicholson et al. (Clin Exp Pharmacol Physiol. 1993; 20: 535-540—reference CT on IDS submitted on 18 August 2006) is maintained for reasons of record (as set forth at pages 10-11 of the Office action mailed 6 November 2006) and the following.

4. Applicants argue at p. 3, 1st full paragraph that claim 1 recites "calculating a relative change in the marker related to the BNP level, and that the relative change in BNP level is defined a the change in the BNP level immediately after exercise as compared to the baseline level, and a baseline BNP level is defined as the BNP

level before a specific event, for example, the BNP level after exercise is compared to a baseline before exercise.

5. Applicants further argue at p. 3, 2nd paragraph that the claim 1 recites the limitation "wherein coronary artery disease is detected if the relative change in the marker related to BNP after cardiac stress is greater than a predetermined clinically effective threshold value, and that paragraph [0057] of the specification clearly states that clinically effective threshold value refers to relative changes in BNP levels with a predetermined threshold value correctly indicating the presence or absence of the disease condition or syndrome, and that resting BNP levels in Nicholson are values corresponding at a point in time before exercise and are not values corresponding to a change in NBP levels, much less to a relative change in BNP levels.
6. Applicants further argue at p. 3, 2nd full paragraph that in Nicholson coronary artery disease is not detected in a mammal if the change in marker related to BNP after cardiac stress is greater than a predetermined clinically effective threshold value, if the predetermined clinically effective threshold value is taken as the resting BNP levels. Applicants point out that looking at plasma BNP basal (resting BNP levels) and BNP peak (BNP levels at exercise completion) for patients 1-16 in Table 1, one could assume that the values imply a change in BNP levels, for example, patient 1 would have a change in BNP level of 8. If the clinically effective threshold value is taken as 27, the resting BNP level for patient 1, patient 1 would not be considered to suffer from coronary heart disease since 8 is less than 27 and that the same

analysis applies to patients 2-16. This method would not detect coronary heart disease in patients 1-16.

7. These arguments have been fully considered, but are not found persuasive for the following reasons. Applicants state that "calculating a relative change in the marker related to the BNP level, and that the relative change in BNP level is defined a the change in the BNP level immediately after exercise as compared to the baseline level, and a baseline BNP level is defined as the BNP level before a specific event, for example, the BNP level after exercise is compared to a baseline before exercise, and Nicholson does exactly that (see Figure 1). Nicholson does compare patients with disease to patients with no disease, which is clear from Figure 1, and at p. 539, left column, last paragraph they state: "[compared] with normal subjects the resting levels of cardiac peptides tended to be increased in our patients with a history of ischemic heart disease...This difference between patient and control was further enhanced during exercise...", thus it flows from this text that a relative change was considered. Because resting and peak exercise levels of ANP and BNP were measured in both diseased and controls, the resting BNP levels of controls recorded in Nicholson et al. could serve as a threshold value, and would meet the definition of "clinically effective threshold value refers to relative changes in BNP levels with a predetermined threshold value correctly indicating the presence or absence of the disease condition or syndrome," as defined at paragraph [0057] of the specification.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action: The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The rejection of claims 1, 9 and 10 under 35 U.S.C. 103(a) as being unpatentable over Nicholson et al. as applied to claims 1, 2, 3, 4, 5, 6, 9, 10, 13, 18, 19, 20, 21 and 22 above, and further in view of Tavel (Chest, 2001; 119: 907-925) as set forth at p. 12 in the Office action mailed 6 November 2006, is maintained for reasons of record and the following.

11. Applicants argue that because the claim limitations are not taught or suggested by Nicholson nor Nicholson in view of Tavel, the rejection under 35 U.SC. 103 falls.

12. This argument has been fully considered but is not found persuasive for the reasons outlined in paragraph 7.

13. The rejection of claims 1, 15, 16 and 17 under 35 U.S.C. 103(a) as being unpatentable over Nicholson et al. as applied to claims 1, 2, 3, 4, 5, 6, 9, 10, 13, 18, 19, 20, 21 and 22 as set forth at pages 10-11 of the Office action mailed 6 November 2006, and further in view of Raza et al. (Inter J Cardio. 2001; 31: 157-167) as set at pages 12 and 13 of the Office action mailed 6 November 2006 is maintained for reasons of record and the following.

14. Applicants argue that because the claim limitations are not taught or suggested by Nicholson nor Nicholson in view of Raza, the rejection under 35 U.SC. 103 falls.

15. This argument has been fully considered but is not found persuasive for the reasons outlined in paragraph 7.

16. The rejection of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 36, 40, 41, 42, 43, 44 under 35 U.S.C. 103(a) as being unpatentable over Marumoto et al. as set forth at pages 3-7 of the in the previous Office action mailed 6 November 2006 is maintained for reasons of record and the following.

17. Applicants argue at p. 6, 1st paragraph that claim 1 recites "calculating a relative change in the marker related to the BNP level, and that "the relative change in BNP level" is defined as "the change in the BNP level immediately after exercise as

compared to the baseline level," and the Examiner is directed to see specification, paragraph [0050], where examples are given. A "baseline BNP" level is defined as "the BNP level before a specific event," for example, "the BNP level after exercise is compared to a baseline BNP level before exercise," see [0050].

18. Applicants assert in the same paragraph that the Examiner's statement that "Figure 2 of Marumoto clearly suggests that taking BNP levels any time from peak exercise to 30 minutes post-exercise would show a difference in BNP levels between healthy and heart diseased patients" is a wholly inaccurate statement.

19. Applicants point out in the same paragraph that Figure 2 plots BNP levels at rest, peak exercise and 30 minutes after exercise. Even if it would have been obvious to measure BNP levels at any time from peak exercise to 30 minutes post-exercise and plot this number in Figure 2, the claim limitation at hand would still not be met, because measuring BNP levels at a time post-cardiac stress does not render obvious calculating a relative change in BNP.

20. Applicants argue at p. 6, 2nd paragraph that claim 1 recites the limitation "wherein coronary artery disease is detected in said mammal if the relative change in marker related to BNP after cardiac stress is greater than a predetermined clinically effective threshold value," and that the term "clinically effective threshold value" is discussed in paragraphs [0053] through [0057] of Applicants' specification, wherein it states: "clinically effective threshold value" refers to relative changes in BNP levels with a predetermined threshold value correctly indicating the presence or absence of the disease, condition, or syndrome. Applicants point out that resting BNP levels in

Marumoto are values corresponding to BNP levels at a point in time, before exercise, and are not values corresponding to a change in BNP levels, much less to a relative change in BNP levels.

21. Applicants argue at p. 7, 1st paragraph that the resting BNP levels in Marumoto are values corresponding to BNP levels at a point in time before exercise, and are not values corresponding to a change in BNP levels, much less to a relative change in BNP levels.

22. At pages 7-8 of their Response, Applicants offer the same arguments to rebut the rejection of independent claim 23 and its dependent claims, but since the arguments are not substantively different than those rebutting claim 1, in the interest of brevity and clarity, all the arguments will be addressed below.

23. Applicants argue that because the claim limitations of 1 and 23 are not met, the rejection under 35 U.S.C 103 of the dependent claims 2-9, 11, 12, 14, 18-22, 24-32, 34, 36 and 40-44 must fall.

24. These arguments have been fully considered but are not found persuasive for the following reasons. Figure 2 of Marumoto clearly shows that BNP levels at rest, peak exercise and 30 minutes after exercise were measured in both diseased and normal individuals. Marumoto clearly suggests that taking measurements immediately after exercise because the difference in the BNP levels between diseased and controls are most striking at immediately following peak exercise, when the distance between the points is the greatest; 30 minutes post exercise, the gap begins to close, although there is still a significant difference. The person of ordinary skill in the art

would clearly have suggestion and motivation to carry out the invention as claimed based on Figure 2, which graphically shows a difference in BNP levels in diseased individuals relative to well individuals post exercise. Interestingly enough, Figure 2 of Marumoto also teaches that BNP levels between diseased and normal individuals are similar, and only increase post exercise in those who are diseased, thus suggesting to the person of ordinary skill in the art that resting levels of BNP in diseased individuals could serve as a threshold, i.e., the sensitivity of the test is in measuring differences after peak exercise, not at rest. Marumoto clearly suggests all the elements of the independent claim, namely measurement of a baseline BNP in diseased and control individuals, motivation to measure the BNP levels immediately post exercise, and a graphical comparison of the relative change (which by necessity, had to have been calculated, since graphs are representations of numerical data). Furthermore, Applicants' argument that the resting BNP levels in Marumoto are values corresponding to BNP levels at a point in time before exercise, and are not values corresponding to a change in BNP levels, much less to a relative change in BNP levels is not persuasive, since Applicants themselves state that a "baseline BNP" level is defined as "the BNP level before a specific event," for example, "the BNP level after exercise is compared to a baseline BNP level before exercise," see [0050] at p. 6, paragraph 1 of their arguments.

25. The rejection of claims 1, 9, 10, 13, 23, 31, 32, 33 and 35 under 35 U.S.C. 103(a) as being unpatentable over Marumoto et al as applied to claims 1, 2, 3, 4, 5, 6, 7, 8,

9, 11, 12, 14, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 36, 40, 41, 42, 43, 44 above, and further in view of Tavel (Tavel, Chest. 2001; 119: 907-925) as set forth at p. 7-9 of the previous Office action mailed 6 November 2006 is maintained for reasons of record and the following.

26. Applicants argue that because the claim limitations are not taught or suggested by Marumoto nor Marumoto in view of Tavel, the rejection under 35 U.SC. 103 falls.

27. This argument has been fully considered but is not found persuasive for the reasons outlined in paragraph 24.

28. The rejection of claims 1, 15, 16, 17, 23, 37, 38, 39 under 35 U.S.C. 103(a) as being unpatentable over Marumoto et al as applied to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 36, 40, 41, 42, 43, 44 above, and further in view of Raza et al. (Inter J Cardio. 2001; 31: 157-167) as set forth at p. 9-10 of the previous Office action mailed 6 November 2006 is maintained for reasons of record and the following.

29. Applicants argue that because the claim limitations are not taught or suggested by Marumoto nor Marumoto in view of Raza, the rejection under 35 U.SC. 103 falls.

30. This argument has been fully considered but is not found persuasive for the reasons outlined in paragraph 24.

Conclusion

31. No claims are allowed.

32. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

33. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest, whose telephone number is 571-272-4482. The examiner can normally be reached on Monday through Friday, 8:00 a.m. to 4:30 p.m.

35. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

36. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Christina Borgeest, Ph.D.

ELIZABETH C. KEMMERER, PH.D.
PRIMARY EXAMINER